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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WITZ, JEAN C

ART UNIT	PAPER NUMBER
1651	

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16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/327,761	Applicant(s) PETERSEN ET AL.	
	Examiner Jean C. Witz	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8 and 12-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,8 and 12-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Applicant's request for reconsideration of the rejection of the last Office action has resulted in the finality of that action being withdrawn. Applicant's arguments with respect to claims of record have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-3, 12-21 and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of O'Leary et al. (5,484,601), Yim et al. (5,385,887) and Gertzman et al. (6,030,635) taken as a whole.

Claim 2 recites a bone graft substitute composition comprising calcium sulfate, a mixing solution, a cellulose derivative and demineralized bone matrix. Dependent claims specify the amounts of the components and recite specific substances that are used for the calcium sulfate component, the mixing solution component and the cellulose derivative component. The specification discloses that the object of the invention is to create a bone graft substitute composition that has "extended set time and sufficient robustness to withstand fluid impact with minimal erosion for expanded

clinical application." Applicants also state that other objects of the invention is to "provide a bone graft substitute composition that can be mixed into a paste and then loaded into a syringe and ejected for an extended period of time (e.g., more than ten minutes)" and to "provide a bone graft substitute composition that can be mixed into a putty and then handled and formed into desired shapes for an extended period of time (e.g., more than ten minutes)."

O'Leary et al. disclose a flowable demineralized bone matrix composition for use in bone repair. O'Leary et al. state at col. 1, lines 36-43 that "[I]t is a particular object of the invention to provide a composition of liquid or pastelike consistency comprising demineralized osteogenic bone powder and a biocompatible liquid synthetic organic material as a carrier for the bone powder with or without such optional ingredients as thixotropic agents, medicaments, and the like, and to apply the composition at a bone defect site to induce new bone ingrowth at the site." At col. 3, lines 14-20, the patent states "[t]o provide the demineralized allogeneic bone powder composition of this invention, the demineralized bone powder with or without any of the foregoing optional components mentioned above absorbed therein is combined with a biocompatible liquid synthetic organic material which functions as a carrier or suspension agent for the bone powder." The patent further defines the terms "liquid" and "flowable" as "intended to include (1) organic materials which in the pure or highly concentrated state and at ambient temperature, e.g., 15-40° C. are flowable liquids and (2) organic materials which in the pure or concentrated state and at ambient temperature are normally solid but dissolved in a suitable solvent, e.g., water or a biocompatible organic

solvent such as ethanol, can be provided in liquid form. Functionally, the liquid component of the composition serves to provide a flowable material of widely varying consistency. The term "flowable" as used herein applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams and fillers." O'Leary et al. disclose at col. 3, line 56 to col. 4, line 6 that "[w]here, in a particular bone powder composition, the bone powder has a tendency to quickly or prematurely separate from the carrier or to otherwise settle out from the composition such that application of a fairly homogeneous composition is rendered difficult or inconvenient, it can be advantageous to include within the composition a substance whose thixotropic characteristics prevent or reduce this tendency. Thus, e.g., where the carrier component is glycerol and separation of bone powder occurs to an excessive extent where a particular application is concerned, a thickener such as a solution of polyvinyl alcohol, polyvinylpyrrolidone, cellulosic ester such as hydroxypropyl methylcellulose, carboxy methylcellulose, pectin, food-grade texturizing agent, gelatin, dextran, collagen, starch, hydrolyzed polyacrylonitrile, hydrolyzed polyacrylamide, polyelectrolyte such as polyacrylic acid salt, etc., can be combined with the carrier in an amount sufficient to significantly improve the suspension-keeping characteristics of the composition. Finally, O'Leary et al. disclose at col. 2, line 53 to col. 3, line 13, that "[a]ny of a variety of substances can be introduced into the bone particles" and includes a non-limiting list which includes inorganic elements,

parenchymal cells, growth factors, bone morphogenic proteins, and mesenchymal elements.

Therefore, O'Leary et al. provides the motivation to produce a bone graft substitute composition containing elements (b)-(d), i.e. a mixing solution, a cellulose derivative and demineralized bone matrix, of claim 2. Further limitations of the claims are also disclosed by the patent. For example, claim 3 requires the present of approximately 40% demineralized bone matrix by dry weight. O'Leary et al. teach at col. 4, lines 18-22 that "[t]he amount of bone powder which can be incorporated into the composition of this invention can vary widely with amounts of from about 5 to about 80 weight percent, and preferably from about 20 to about 60 weight percent, being entirely suitable in most cases." Claims 16-17 define the specific cellulose derivatives. Cellulosic esters such as hydroxypropyl methylcellulose and carboxy methylcellulose, both of which are recited in claims 16 and 17, are identified as included in the composition of O'Leary as a thixotropic agent.

While there is no explicit disclosure of the presence of calcium sulfate or bone allograft, it is noted that the O'Leary patent clearly teaches that "any variety of substances" can be introduced to the composition include "inorganic elements".

Yim et al. discloses a composition for delivery of osteogenic proteins. The patent states that "the subject invention involves pharmaceutical formulations designed to sequester osteogenic protein in situ for a time sufficient to allow the protein to induce cartilage and/or bone formation." Yim et al. teach that "[o]steogenic proteins are those proteins capable of inducing, or assisting in the induction of, cartilage and/or

bone formation. Many such osteogenic proteins have in recent years been isolated and characterized, and some have been produced by recombinant methods. For example, so-called bone morphogenic proteins (BMP) have been isolated from demineralized bone tissue." Yim et al. further teach that "[I]n U.S. Pat. No. 5,171,579, it is disclosed that osteogenic proteins can be sequestered at a site where bone inducing activity is desired using autogenous blood, without using antifibrinolytic agents, provided that a porous particulate polymer matrix is incorporated into the formulation. To reduce the preparation time and improve the above formulation's handling characteristics, [Patentees] have surprisingly found that it is desirable to add a calcium sulfate hemihydrate-containing substance (CSHS). The CSHS is preferably either pure calcium sulfate hemihydrate, also known as Plaster of Paris (POP), or a mixture of POP and hydroxyapatite (POP:HA). Adding a CSHS reduces setup time and provides improved moldability and consistency of the resulting formulation.

Yim et al. state that the osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution and cites sodium chloride as an appropriate solubilizing agent, as well as multiple different aqueous solutions of amino acids and other acids. See col. 3, line 53. Further, at col. 4, lines 32-33, the osteogenic protein formulations may be lyophilized and reconstituted with water prior to use. Yim et al. also include a "porous particulate polymer matrix component" that acts as an "in situ scaffolding for the osteogenic protein, while having biodegradable properties allowing for replacement by new bone growth" as well as a "protein-sequestering material". This material is used to "hold" the osteogenic proteins at the site for a sufficient time to

allow them to have a bone growth promoting effect. This may be a blood clot from autogenous blood. Yim et al. states that "[i]n the absence of such blood clot, osteogenic protein desorbs from the [particulate polymer matrix] particles in situ at a rate such that the osteoinducing effect of the protein is not clinically significant." Suitable "protein-sequestering agents" are disclosed at col. 7, lines 25-34, as cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose." The cellulosic protein sequestering agent is preferably present in a concentration of about 2 to about 10% (w/v). Determination of the quantity of the calcium sulfate hemihydrate is disclosed as being well within the skill of the practitioner and is determined to be that quantity which provides the best handling properties both immediately after and 1 to 2 hours after preparation will be optimal. The formulations of the disclosure of Yim et al. provide "malleable implants that allow therapeutically effective amounts of osteoinductive protein to be delivered to an injury site where cartilage and/or bone formation is desired. Such an implant may be used as a substitute for autologous bone graft in fresh and non-union fractures, spinal fusions, and bone defect repair in the orthopaedic field; in cranio/maxillofacial reconstructions; for prosthesis integration, especially as a surface coating to improve fixation of prosthetic implants such as hydroxylapatite coated prostheses; in osteomyelitis for bone regeneration; and in the dental field for augmentation of the alveolar ridge and periodontal defects and tooth extraction sockets. When used to treat osteomyelitis or for bone repair with minimal infection, the

osteogenic protein may be used in combination with porous microparticles and antibiotics, with the addition of protein sequestering agents such as alginate, cellulosics, especially carboxymethylcellulose, diluted using aqueous glycerol. The antibiotic is selected for its ability to decrease infection while having minimal adverse effects on bone formation. Preferred antibiotics for use in the devices of the present invention include vancomycin and gentamycin. The antibiotic may be in any pharmaceutically acceptable form, such as vancomycin HCl or gentamycin sulfate. The antibiotic is preferably present in a concentration of from about 0.1 mg/mL to about 10.0 mg/mL. The lower viscosity formulations may also be used as a percutaneous injection to accelerate healing of closed fractures. In certain of these uses, the compositions of the subject invention may be used in combination with various bone cements, including erodible bone cements such as poly(propylene-co-fumarate) and certain hydroxyapatite cements. Also, certain of these uses will utilize bioerodible hardware such as erodible plates, screws, etc. As alluded to above, the dosage regimen will be determined by the clinical indication being addressed, as well as by various patient variables (e.g. weight, age, sex) and clinical presentation (e.g. extent of injury, site of injury, etc.). In general, the dosage of osteogenic protein will be in the range of from about 10 to 1000 μg, preferably from about 10 to 100 μg."

Therefore, Yim et al. provides the disclosure of a bone graft substitute composition containing elements (a)-(c), i.e. calcium sulfate, a mixing solution, and a cellulose derivative, of claim 2. The bone morphogenic proteins of the Yim reference, while not identical in composition to demineralized bone matrix of the claims, serves

the same purpose, i.e. the delivery of bone growth promoting proteins to a site of bone injury. As noted previously, bone morphogenic proteins are present in demineralized bone matrix. Further limitations of the claims are also disclosed by the patent. For example, claims 13-15 require specific mixing solutions. Yim et al. discloses, in a non-limiting list, both water and sodium chloride as a solvent present in the composition for the osteogenic proteins. Since calcium sulfate hemihydrate (plaster of paris) requires an aqueous solution to activate it and allow it to harden, one of ordinary skill in the art would be aware that the aqueous osteogenic protein solution would act both to solubilized the osteogenic proteins and to activate the calcium sulfate hemihydrate as would the aquous component of autogenous blood, present at the site of the injury. Claim 20 requires the present of approximately approximately 3% carboxymethylcellulose by weight. Yim et al. teaches at col. 7, lines 40-45, that the cellulosic protein sequestering agent is preferably present in 2-10% (w/v). Claims 16-17 define the specific cellulose derivatives. Cellulosic materials such as recited in claims 16 and 17, are identified as included in the composition of Yim et al. as a protein sequestering agent.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of O'Leary et al. with components of the composition of Yim et al. Both O'Leary et al. and Yim et al. have the same object in creating a malleable, workable bone growth promoting composition. One of ordinary skill in the art when reviewing the disclosure of Yim would have been motivated to include a calcium sulfate component into the composition of O'Leary et al.

with the expected benefit disclosed by Yim et al., i.e. that a calcium sulfate component would add improved handling, moldibility and consistency to the formulation of O'Leary as well as reducing the set up time. The compositions of Yim and O'Leary are so sufficiently similar that one of ordinary skill in the art at the time the invention was made would be aware of the properties of the calcium sulfate hemihydrate would not impair or otherwise negatively affect the components of the O'Leary composition. Both compositions contain components that provide either directly or indirectly osteogenic proteins, and both compositions contain a cellulosic material which is being used for the same purpose, i.e. to impart viscosity and suspension properties to the respective compositions. With regard to claim 12, the general amounts of both the demineralized bone matrix and the cellulose material are taught by the references. The optimization of the amount of calcium sulfate and mixing solution to be further included is deemed well within the skill of the practitioner at the time the invention was made as it is clear that the amount of calcium sulfate is directly related to desired rate of set up of the composition, i.e. the more calcium sulfate used, the faster the composition will set up and harden. Further, it is clear that the amount of mixing solution is inversely related to the desired set up time and directly proportional to the ultimate consistency of the composition, i.e. the more mixing solution used, the more dilute the calcium sulfate and the slower the set up time but the more liquid the composition will become.

Finally, claim 21 recites the further inclusion of a bone allograft. Both patents teach that other conventional components included in bone growth promoting compositions may be included in the disclosed compositions. The patent to

Gertzmann et al. teaches another malleable paste composition for filling bone defects. In the Background of the Invention, the reference teaches at col. 1 the various substances known to be included in a bone growth promoting composition. Included in this list is autologous bone, bone marrow, blood, calcium sulfate, and allograft bone. The inclusion of allograft bone for the addition of the "building blocks" of new bone, i.e. collagen fiber reinforced hydroxyapatite matrix containg active bone morphogenic proteins at an area so treated is well within the skill of the practitioner in order to maximize the bone growth promoting activity of the composition.

With regard to claims 35-38, the patent to Yim et al. clearly acknowledges that a composition containing calcium sulfate hemihydrate must be kept dry until the time of its use since the addition of an aqueous solution causes the activation of the calcium sulfate hemihydrate and results in ultimate hardening of the calcium sulfate hemihydrate (such as seen with the use of plaster of paris). Yim et al. state at col. 8 that "[t]he osteogenic protein and porous particles of the formulations may be provided to the clinic as a single vial formulation, either as a solution or in lyophilized form, or the formulation may be provided as a multicomponent kit wherein, e.g. the osteogenic protein is provided in one vial and the porous particles and calcium sulfate hemihydrate-containing substance each are provided in separate vials. The blood to be used in the formulation is admixed at a time prior to use sufficient to allow clotting, generally 15 to 180 minutes prior to use, taking into account the well-known patient-to-patient variability in clotting time, as well as the ability of CSHS to accelerate

formability of the device." One of ordinary skill in the art would be aware that if lyophilized or powdered, the bone morphogenic protein could be mixed with the calcium sulfate and the cellulose derivative (and optionally, the bone allograft) first in order to provide a homogeneous distribution and then adding the mixing solution to activate the calcium sulfate hemihydrate. While Yim et al. includes blood, this is not deemed to affect any of the above noted motivations to produce the claimed composition since it is noted that (1) the blood is used for a dual purpose as both an activator and in order to provide a fibrin clot to further assist in keeping the bone growth promoting composition at the site of the injury; (2) autologous blood would be expected to be present and act in the same manner in the practice of Applicants' invention and (3) the claims are couched in open language which does not preclude the inclusion of other unspecified components. Further, Yim et al. discloses the mixing of the osteogenic proteins in solution with the calcium sulfate hemihydrate. The aqueous solvent of the osteogenic proteins, such as water or sodium chloride, would be expected to activate the calcium sulfate hemihydrate. When including the calcium sulfate hemihydrate component into the composition of O'Leary et al., one of ordinary skill in the art would be aware and motivated to provide an aqueous activating mixing solution since the bone morphogenic proteins are contained within the dry demineralized bone matrix and the practitioner could not rely on the above mentioned solvent to act also as an activator.

Claims 8 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Leary et al. (5,484,601), Yim et al. (5,385,887) and Gertzman et al. (6,030,635) taken as a whole.

Claim 8 recites a bone graft substitute composition comprising calcium sulfate, a mixing solution, a cellulose derivative and a bioactive agent selected from the group consisting of growth factors, bone autograft, analgesics, bone marrow, bone allograft, and parenchymal and mesenchymal cells. Dependent claims recite specific substances that are used for the calcium sulfate component, the mixing solution component and the cellulose derivative component. The specification discloses that the object of the invention is to create a bone graft substitute composition that has "extended set time and sufficient robustness to withstand fluid impact with minimal erosion for expanded clinical application." Applicants also state that other objects of the invention is to "provide a bone graft substitute composition that can be mixed into a paste and then loaded into a syringe and ejected for an extended period of time (e.g., more than ten minutes)" and to "provide a bone graft substitute composition that can be mixed into a putty and then handled and formed into desired shapes for an extended period of time (e.g., more than ten minutes)."

O'Leary et al. disclose a flowable demineralized bone matrix composition for use in bone repair. O'Leary et al. state at col. 1, lines 36-43 that "[I]t is a particular object of the invention to provide a composition of liquid or pastelike consistency comprising demineralized osteogenic bone powder and a biocompatible liquid synthetic organic material as a carrier for the bone powder with or without such optional ingredients as

thixotropic agents, medicaments, and the like, and to apply the composition at a bone defect site to induce new bone ingrowth at the site." At col. 3, lines 14-20, the patent states "[t]o provide the demineralized allogeneic bone powder composition of this invention, the demineralized bone powder with or without any of the foregoing optional components mentioned above absorbed therein is combined with a biocompatible liquid synthetic organic material which functions as a carrier or suspension agent for the bone powder." The patent further defines the terms "liquid" and "flowable" as "intended to include (1) organic materials which in the pure or highly concentrated state and at ambient temperature, e.g., 15-40° C. are flowable liquids and (2) organic materials which in the pure or concentrated state and at ambient temperature are normally solid but dissolved in a suitable solvent, e.g., water or a biocompatible organic solvent such as ethanol, can be provided in liquid form. Functionally, the liquid component of the composition serves to provide a flowable material of widely varying consistency. The term "flowable" as used herein applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams and fillers." O'Leary et al. disclose at col. 3, line 56 to col. 4, line 6 that "[w]here, in a particular bone powder composition, the bone powder has a tendency to quickly or prematurely separate from the carrier or to otherwise settle out from the composition such that application of a fairly homogeneous composition is rendered difficult or inconvenient, it can be advantageous to include within the composition a substance

whose thixotropic characteristics prevent or reduce this tendency. Thus, e.g., where the carrier component is glycerol and separation of bone powder occurs to an excessive extent where a particular application is concerned, a thickener such as a solution of polyvinyl alcohol, polyvinylpyrrolidone, cellulosic ester such as hydroxypropyl methylcellulose, carboxy methylcellulose, pectin, food-grade texturizing agent, gelatin, dextran, collagen, starch, hydrolyzed polyacrylonitrile, hydrolyzed polyacrylamide, polyelectrolyte such as polyacrylic acid salt, etc., can be combined with the carrier in an amount sufficient to significantly improve the suspension-keeping characteristics of the composition. Finally, O'Leary et al. disclose at col. 2, line 53 to col. 3, line 13, that "[a]ny of a variety of substances can be introduced into the bone particles" and includes a non-limiting list which includes inorganic elements, parenchymal cells, growth factors, bone morphogenic proteins, and mesenchymal elements.

Therefore, O'Leary et al. provides the motivation to produce a bone graft substitute composition containing elements (b)-(d), i.e. a mixing solution, a cellulose derivative and a bioactive agent such as a growth factor, parenchymal cells or mesenchymal cells of claim 8. Further limitations of the claims are also disclosed by the patent. Claims 25-26 define the specific cellulose derivatives. Cellulosic esters such as hydroxypropyl methylcellulose and carboxy methylcellulose, both of which are recited in claims 25 and 26, are identified as included in the composition of O'Leary as a thixotropic agent.

While there is no explicit disclosure of the presence of calcium sulfate, bone autograft, analgesics, bone marrow or bone allograft, it is noted that the O'Leary patent clearly teaches that "any variety of substances" can be introduced to the composition include "inorganic elements".

Yim et al. discloses a composition for delivery of osteogenic proteins. The patent states that "the subject invention involves pharmaceutical formulations designed to sequester osteogenic protein in situ for a time sufficient to allow the protein to induce cartilage and/or bone formation." Yim et al. teach that "[o]steogenic proteins are those proteins capable of inducing, or assisting in the induction of, cartilage and/or bone formation. Many such osteogenic proteins have in recent years been isolated and characterized, and some have been produced by recombinant methods. For example, so-called bone morphogenic proteins (BMP) have been isolated from demineralized bone tissue." Yim et al. further teach that "[I]n U.S. Pat. No. 5,171,579, it is disclosed that osteogenic proteins can be sequestered at a site where bone inducing activity is desired using autogenous blood, without using antifibrinolytic agents, provided that a porous particulate polymer matrix is incorporated into the formulation. To reduce the preparation time and improve the above formulation's handling characteristics, [Patentees] have surprisingly found that it is desirable to add a calcium sulfate hemihydrate-containing substance (CSHS). The CSHS is preferably either pure calcium sulfate hemihydrate, also known as Plaster of Paris (POP), or a mixture of POP and hydroxyapatite (POP:HA). Adding a CSHS reduces setup time and provides improved moldability and consistency of the resulting formulation.

Yim et al. state that the osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution and cites sodium chloride as an appropriate solubilizing agent, as well as multiple different aqueous solutions of amino acids and other acids. See col. 3, line 53. Further, at col. 4, lines 32-33, the osteogenic protein formulations may be lyophilized and reconstituted with water prior to use. Yim et al. also include a "porous particulate polymer matrix component" that acts as an "in situ scaffolding for the osteogenic protein, while having biodegradable properties allowing for replacement by new bone growth" as well as a "protein-sequestering material". This material is used to "hold" the osteogenic proteins at the site for a sufficient time to allow them to have a bone growth promoting effect. This may be a blood clot from autogenous blood. Yim et al. states that "[i]n the absence of such blood clot, osteogenic protein desorbs from the [particulate polymer matrix] particles in situ at a rate such that the osteoinducing effect of the protein is not clinically significant." Suitable "protein-sequestering agents" are disclosed at col. 7, lines 25-34, as cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose." The cellulosic protein sequestering agent is preferably present in a concentration of about 2 to about 10% (w/v). Determination of the quantity of the calcium sulfate hemihydrate is disclosed as being well within the skill of the practitioner and is determined to be that quantity which provides the best handling properties both immediately after and 1 to 2 hours after preparation will be optimal. The formulations of the disclosure of Yim et al. provide

"malleable implants that allow therapeutically effective amounts of osteoinductive protein to be delivered to an injury site where cartilage and/or bone formation is desired. Such an implant may be used as a substitute for autologous bone graft in fresh and non-union fractures, spinal fusions, and bone defect repair in the orthopaedic field; in cranio/maxillofacial reconstructions; for prosthesis integration, especially as a surface coating to improve fixation of prosthetic implants such as hydroxylapatite coated prostheses; in osteomyelitis for bone regeneration; and in the dental field for augmentation of the alveolar ridge and periodontal defects and tooth extraction sockets. When used to treat osteomyelitis or for bone repair with minimal infection, the osteogenic protein may be used in combination with porous microparticles and antibiotics, with the addition of protein sequestering agents such as alginate, cellulosics, especially carboxymethylcellulose, diluted using aqueous glycerol. The antibiotic is selected for its ability to decrease infection while having minimal adverse effects on bone formation. Preferred antibiotics for use in the devices of the present invention include vancomycin and gentamycin. The antibiotic may be in any pharmaceutically acceptable form, such as vancomycin HCl or gentamycin sulfate. The antibiotic is preferably present in a concentration of from about 0.1 mg/mL to about 10.0 mg/mL. The lower viscosity formulations may also be used as a percutaneous injection to accelerate healing of closed fractures. In certain of these uses, the compositions of the subject invention may be used in combination with various bone cements, including erodible bone cements such as poly(propylene-co-fumarate) and certain hydroxyapatite cements. Also, certain of these uses will utilize bioerodible

hardware such as erodible plates, screws, etc. As alluded to above, the dosage regimen will be determined by the clinical indication being addressed, as well as by various patient variables (e.g. weight, age, sex) and clinical presentation (e.g. extent of injury, site of injury, etc.). In general, the dosage of osteogenic protein will be in the range of from about 10 to 1000 μg, preferably from about 10 to 100 μg."

Therefore, Yim et al. provides the disclosure of a bone graft substitute composition containing elements (a)-(c), i.e. calcium sulfate, a mixing solution, and a cellulose derivative, of claim 2. The bone morphogenic proteins of the Yim reference, while not identical in composition to bioactive agent such as bone autograft, bone marrow or bone allograft of the claims, would be expected to serve the same purpose, i.e. the delivery of bone growth promoting proteins to a site of bone injury, as all of these components are known to contain bone morphogenic proteins – see the disclosure of Gertzman et al. infra. With regard to claims 22-24 which require specific mixing solutions, since calcium sulfate hemihydrate (plaster of paris) requires an aqueous solution to activate it and allow it to harden, one of ordinary skill in the art would be aware that any physiologically compatible aqueous solutions would be necessary to activate the calcium sulfate hemihydrate. Claims 25-26 define the specific cellulose derivatives. Cellulosic materials such as recited in claims 25 and 26 are identified as included in the composition of Yim et al. as a protein sequestering agent.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of O'Leary et al. with

components of the composition of Yim et al. Both O'Leary et al. and Yim et al. have the same object in creating a malleable, workable bone growth promoting composition. One of ordinary skill in the art when reviewing the disclosure of Yim would have been motivated to include a calcium sulfate component into the composition of O'Leary et al. with the expected benefit disclosed by Yim et al., i.e. that a calcium sulfate component would add improved handling, moldibility and consistency to the formulation of O'Leary as well as reducing the set up time. The compositions of Yim and O'Leary are so sufficiently similar that one of ordinary skill in the art at the time the invention was made would be aware of the properties of the calcium sulfate hemihydrate would not impair or otherwise negatively affect the components of the O'Leary composition. Both compositions contain components that provide either directly or indirectly osteogenic proteins, and both compositions contain a cellulosic material which is being used for the same purpose, i.e. to impart viscosity and suspension properties to the respective compositions.

Finally, claims 28-34 recite the further inclusion of individually specified bioactive components. Both patents teach that other conventional components included in bone growth promoting compositions may be included in the disclosed compositions. As discussed above, O'Leary et al. disclose the inclusion of growth factors, parenchymal cells and mesenchymal elements, a group of which mesenchymal cells are a member. The patent to Gertzmann et al. teaches another malleable paste composition for filling bone defects. In the Background of the Invention, the reference teaches at col. 1 the various substances known to be included in a bone growth promoting composition.

Included in this list is autologous bone, bone marrow, blood, calcium sulfate, and allograft bone. The inclusion of any of the disclosed bioactive agents into the claimed composition is deemed well within the skill of the practitioner as each component is well known to be used for bone growth promotion. The inclusion of analgesics into any surgical composition is deemed well within the skill of the practitioner for the expected result of reducing pain at the surgical site. The inclusion of bioactive agents such as autologous bone and allograft bone for the addition of the "building blocks" of new bone, i.e. collagen fiber reinforced hydroxyapatite matrix containg active bone morphogenic proteins at an area so treated is well within the skill of the practitioner in order to maximize the bone growth promoting activity of the composition.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (703) 308-3073. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-Th and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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